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(54) Title: METHODS OF USING A SOMATOSTATIN ANALOGUE

(57) Abstract

The present invention is directed to a method of treating one or more of the following disease and/or conditions, which comprises administering to a patient in need thereof the compound H–g(b)–D–Nal–Cys–Tyr–D–Trp–Lys–Val–Cys–Thr–NH_2, where the Cysteines are bonded by a disulfide bond, or a pharmaceutically acceptable salt thereof, most preferably the acetate salt of the compound, in the treatment of certain diseases and/or conditions such as gastroenterological conditions and/or diseases, endocronological diseases and/or conditions, various types of cancers and conditions associated with cancer such as cancer cachexia and in the treatment of hypotension and panic attacks.

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METHODS OF USING A SOMATOSTATIN ANALOGUE

Background of the Invention

The present invention is directed to a method of treating one or more of the following diseases and/or conditions in a patient in need thereof, which comprises the administration of the compound of the formula H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2 (also known as lanreotide), where the two Cysteines are bonded by a disulfide bond, or a pharmaceutically acceptable salt thereof, most preferably the acetate salt of the compound, in the treatment of certain diseases and/or conditions such as gastroenterological conditions and/or diseases, such as Crohn's disease, systemic sclerosis, external and internal pancreatic pseudocysts and ascites, VIPoma, nesidoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison Syndrome, diarrhea, AIDS related diarrhea, chemotherapy related diarrhea, scleroderma, Irritable Bowel Syndrome, pancreatitis, upper gastrointestinal bleeding, postprandial portal venous hypertension especially in cirrhotic patients, complications of portal hypertension, small bowel obstruction, gastroesophageal reflux, duodenogastric reflux and in treating endocrinological diseases and/or conditions, such as Cushing's Syndrome, gonadotropinoma, hyperparathyroidism, Graves' Disease, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy, Paget's disease, and polycystic ovary disease; in treating various types of cancer such as thyroid cancer, leukemia, meningioma and conditions associated with cancer such as cancer cachexia; in the treatment of such conditions as hypotension such as orthostatic hypotension and postprandial hypotension and panic attacks.

Lanreotide is an analog of somatostatin and is known to inhibit growth hormone release as well as inhibit insulin, glucagon and pancreatic exocrine secretion.

U.S. Patent No. 4,853,371 discloses lanreotide, a method for making it and a method for inhibiting the secretion of growth hormone, insulin, glucagon and pancreatic exocrine secretion.

U.S. Patent No. 5,147,856 discloses the use of lanreotide of treating restenosis.

U.S. Patent No. 5,411,943 discloses the use of lanreotide for treating hepatoma.

U.S. Patent No. 5,073,541 discloses the use of lanreotide for treating lung cancer.

U.S. Application No. 08/089,410 filed July 9, 1993 discloses the use of lanreotide for treating melanoma.

U.S. Patent No. 5,504,069 discloses the use of lanreotide for inhibiting the accelerated growth of a solid tumor.

U.S. Application No. 08/854,941 filed May 13, 1997, discloses the use of lanreotide for decreasing body weight.

U.S. Application No. 08/854,943 filed May 13, 1997, discloses the use of lanreotide for treating insulin resistance and Syndrome X.

U.S. Patent No. 5,688,418 discloses the use of lanreotide for prolonging the survival of pancreatic cells.

PCT Application No. PCT/US97/14154 discloses the use of lanreotide for treating fibrosis.

U.S. Application No. 08/855,311 filed May 13, 1997, discloses the use of lanreotide for treating hyperlipidemia.

U.S. Application No. 08/440,061 filed May 12, 1995, discloses the use of lanreotide for treating hyperamylinemia.

U.S. Application No. 08/852,221 filed May 7, 1997, discloses the use of lanreotide for treating hyperprolactinemia and prolactinomas.

The contents of the foregoing patents and applications are incorporated herein by reference.

Summary of the Invention

This invention is directed to a method of treating a disease or condition which comprises administering to a patient in need thereof an effective amount of the compound H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2, where the two Cysteines are bonded by a disulfide bond, or a pharmaceutically acceptable salt thereof, wherein the disease or condition is selected from the group consisting of systemic sclerosis, pancreatic pseudocysts, pancreatic ascites, VIPoma, nesidoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison Syndrome, hypersecretory diarrhea, scleroderma, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal venous hypertension, complications of portal hypertension, small bowel obstruction, duodenogastric reflux, Cushing's

Syndrome, gonadotropinoma, hyperparathyroidism, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy, Paget's disease, meningioma, cancer cachexia, psoriasis, hypotension and panic attacks.

A preferred method of the immediately foregoing method is where the acetate salt of H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2 is administered.

A preferred method of the immediately foregoing method is where the disease or condition is selected from the group consisting of VIPoma, nesidoblastosis, hyperinsulinism, gastrinoma, hypersecretory diarrhea, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal venous hypertension, especially in cirrhotic patients, complications of portal hypertension, small bowel obstruction, diabetic neuropathy, meningioma and cancer cachexia.

A preferred method of the immediately foregoing method is where the disease or condition treated is selected from the group consisting of VIPoma, nesidoblastosis, hypersecretory diarrhea, irritable bowel syndrome, small bowel obstruction and diabetic neuropathy.

In another aspect, the present invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of the acetate salt of H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2 to treat a disease or condition wherein the disease or condition is selected from the group consisting of systemic sclerosis, pancreatic pseudocysts, pancreatic ascites, VIPoma, nesidoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison Syndrome, hypersecretory diarrhea, scleroderma, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal venous hypertension, especially in cirrhotic patients, complications of portal hypertension, small bowel obstruction, duodenogastric reflux, Cushing's Syndrome, gonadotropinoma, hyperparathyroidism, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy, Paget's disease, meningioma, cancer cachexia, psoriasis, hypotension and panic attacks.

Detailed Description

Lanreotide is readily prepared according to the procedure disclosed in U.S. Patent No. 4,853,371, or the procedure disclosed in U.S. Patent No. 5,411,943, the teachings of which are incorporated herein by reference.

Lanreotide is currently marketed as the acetate salt in a 30 mg long-acting form and is available from Ipsen Biotech, Paris, France.

As is well known to those skilled in the art, the known and potential uses of somatostatin are varied and multitudinous. Somatostatin is known to be useful in the treatment of the diseases and/or conditions listed hereinbelow. The varied uses of somatostatin may be summarized as follows: Cushings Syndrome (see Clark, R.V. et al, Clin. Res. 38, p. 943A, 1990); gonadotropinoma (see Ambrosi B., et al., Acta Endocr. (Copenh.) 122, 569-576, 1990); hyperparathyroidism (see Miller, D., et al., Canad. Med. Ass. J., Vol. 145, pp. 227-228, 1991); Paget's disease (see, Palmieri, G.M.A., et al., J. of Bone and Mineral Research, 7, (Suppl. 1), p. S240 (Abs. 591), 1992); VIPoma (see Koberstein, B., et al., Z. Gastroenterology, 28, 295-301, 1990 and Christensen, C., Acta Chir. Scand. 155, 541-543, 1989); nesidioblastosis and hyperinsulinism (see Laron, Z., Israel J. Med. Sci., 26, No. 1, 1-2, 1990, Wilson, D.C., Irish J. Med. Sci., 158, No. 1, 31-32, 1989 and Micic, D., et al., Digestion, 16, Suppl. 1.70. Abs. 193, 1990); gastrinoma (see Bauer, F.E., et al., Europ. J. Pharmacol., 183, 55 1990); Zollinger-Ellison Syndrome (see Mozell, E., et al., Surg. Gynec. Obstet., 170, 476-484, 1990); hypersecretory diarrhea related to AIDS and other conditions (due to AIDS, see Cello, J.P., et al., Gastroenterology, 98, No. 5, Part 2, Suppl., A163 1990; due to elevated gastrin-releasing peptide, see Alhindawi, R., et al., Can. J. Surg., 33, 139-142, 1990; secondary to intestinal graft vs. host disease, see Bianco J.A., et al., Transplantation, 49, 1194-1195, 1990; diarrhea associated with chemotherapy, see Petrelli, N., et al., Proc. Amer. Soc. Clin. Oncol., Vol. 10, P 138, Abstr. No. 417 1991); irritable bowel syndrome (see O'Donnell, L.J.D., et al., Aliment. Pharmacol. Therap., Vol. 4., 177-181, 1990); pancreatitis (see Tulassay, Z., et al., Gastroenterology, 98, No. 5, Part 2, Suppl., A238, 1990); Crohn's Disease (see Fedorak, R.N., et al., Can. J. Gastroenterology, 3, No. 2, 53-57, 1989); systemic sclerosis (see Soudah, H., et al., Gastroenterology, 98, No. 5, Part 2, Suppl., A129, 1990); thyroid cancer (see Modigliani, E., et al., Ann., Endocr. (Paris), 50, 483-488, 1989); psoriasis (see Camisa, C., et al., Cleveland Clinic J. Med., 57 ,No. 1, 71-76, 1990); hypotension (see Hoeldtke, R.D., et al., Arch. Phys. Med. Rehabil., 69, 895-898, 1988 and Kooner, J.S., et al., Brit. J. Clin. Pharmacol., 28, 735P-736P, 1989); panic attacks (see Abelson, J.L., et al., Clin. Psychopharmacol., 10, 128-132, 1990); sclerodoma (see Soudah, H., et al., Clin. Res., Vol. 39, p. 303A, 1991);

small bowel obstruction (see Nott, D.M., et al., Brit. J. Surg., Vol. 77, p. A691, 1990); gastroesophageal reflux (see Branch, M.S., et al., Gastroenterology, Vol. 100, No. 5, Part 2 Suppl., p. A425, 1991); duodenogastric reflux (see Hasler, W., et al., Gastroenterology, Vol. 100, No. 5, Part 2, Suppl., p. A448, 1991); Graves' Disease (see Chang, T.C., et al., Brit. Med. J., 304, p. 158, 1992); polycystic ovary disease (see Prelevic, G.M., et al., Metabolism Clinical and Experimental, 41, Suppl. 2, pp 76-79, 1992); upper gastrointestinal bleeding (see Jenkins, S.A., et al., Gut., 33, pp. 404-407, 1992 and Arrigoni, A., et al., American Journal of Gastroenterology, 87, p. 1311, (abs. 275), 1992); pancreatic pseudocysts and ascites (see Hartley, J.E., et al., J. Roy. Soc. Med., 85, pp. 107-108, 1992); leukemia (see Santini, et al., 78, (Suppl. 1), p. 429A (Abs. 1708), 1991); meningioma (see Koper, J.W., et al., J. Clin. Endocr. Metab., 74, pp. 543-547, 1992); and cancer cachexia (see Bartlett, D.L., et al., Surg. Forum., 42, pp. 14-16, 1991). The contents of the foregoing references are incorporated herein by reference.

Surprisingly, the Applicant has now discovered that lanreotide itself was particularly useful in treating the conditions, disorders and disease noted hereinabove.

The usefulness of lanreotide in the various disclosed new medical uses can be better understood through the results of tests relating to the treatment of upper gastrointestinal bleeding.

Lanreotide or a pharmaceutically-acceptable salt thereof can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous or subcutaneous injection, or implant), nasal, vaginal, rectal, sublingual or topical routes of administration and can be formulated with pharmaceutically acceptable carriers to provide dosage forms appropriate for each route of administration.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, by irradiating the compositions, or by heating the compositions. They can also be manufactured in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as coca butter or a suppository wax.

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

The dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. Generally, dosage levels of between 25 ?g/kg/day to 100 mg/kg/day of body weight daily are administered as a single dose or divided into multiple doses to humans and other animals, e.g., mammals, to obtain the desired therapeutic effect.

A preferred general dosage range is 250 ?g/kg/day to 5.0 mg/kg/day of body weight daily which can be administered as a single dose or divided into multiple doses.

Further, Lanreotide can be administered in a sustained release composition such as those described in the following patents. Among those formulations, 14-day or 28-day slow release formulations will be preferred. U.S.

Patent No. 5,672,659 teaches sustained release compositions comprising Lanreotide and a polyester. U.S. Patent No. 5,595,760 t aches sustained release compositions comprising Lanreotide in a gelable form. U.S. Application No. 08/929,363 filed September 9, 1997, teaches polymeric sustained release compositions comprising Lanreotide and chitosan. U.S. Application No. 08/740,778 filed November 1, 1996, teaches sustained release compositions comprising Lanreotide and cyclodextrin. U.S. Application No. 09/015,394 filed January 29, 1998, teaches absorbable sustained release compositions of Lanreotide. The contents of the foregoing patents and applications are incorporated herein by reference.

The use of immediate or of sustained release compositions depends on the type of indications aimed at. If the indication consists of an acute or over-acute disorder, a treatment with an immediate form will be preferred over the same with a prolonged release composition. On the contrary, for preventive or long-term treatments, a prolonged release composition will generally be preferred.

Typically, to the indication upper gastrointestinal bleeding will correspond an acute or over-acute treatment with a dosage of 80 to 120 ?g/day per person during approximately 5 days. After endoscopical treatment, preventive treatment against recurrence can be performed using lanreotide sustained release forms as an adjuvant to usual treatments; for this type of treatment, 14-day sustained release forms with a total dosage of approximately 30 mg lanreotide or 28-day lanreotide forms can be used.

For other indications than upper gastrointestinal bleeding, which correspond rather long term treatments, 14-day sustained release forms with a total dosage of approximately 30 mg lanreotide or 28-day lanreotide forms will be adequate.

Claims

1. A method of treating a disease or condition which comprises administering to a patient in need thereof an effective amount of the compound H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2, where the two Cysteines are bonded by a disulfide bond, or a pharmaceutically acceptable salt thereof, wherein the disease or condition is selected from the group consisting of systemic sclerosis, pancreatic pseudocysts, pancreatic ascites, VIPoma, nesidoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison Syndrome, hypersecretory diarrhea, scleroderma, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal venous hypertension, complications of portal hypertension, small bowel obstruction, duodenogastric reflux, Cushing's Syndrome, gonadotropinoma, hyperparathyroidism, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy, Paget's disease, meningioma, cancer cachexia, psoriasis, hypotension and panic attacks.

2. A method according to claim 1 wherein the acetate salt of H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2 is administered.

3. A method according to claim 2 wherein the disease or condition is selected from the group consisting of VIPoma, nesidoblastosis, hyperinsulinism, gastrinoma, hypersecretory diarrhea, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal venous hypertension, especially in cirrhotic patients, complications of portal hypertension, small bowel obstruction, diabetic neuropathy, meningioma and cancer cachexia.

4. A method according to claim 3 wherein the disease or condition treated is selected from the group consisting of VIPoma, nesidoblastosis, hypersecretory diarrhea, irritable bowel syndrome, small bowel obstruction and diabetic neuropathy.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of the acetate salt of H-β-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2 to treat a disease or condition wherein the disease or condition is selected from the group consisting of systemic sclerosis, pancreatic pseudocysts, pancreatic ascites, VIPoma, nesidoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison Syndrome, hypersecretory diarrhea, scleroderma, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal venous hypertension, especially in cirrhotic patients, complications of portal hypertension, small bowel obstruction, duodenogastric

reflux, Cushing's Syndrome, gonadotropinoma, hyperparathyroidism, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy, Paget's disease, meningioma, cancer cachexia, psoriasis, hypotension and panic attacks.

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(57) Abstract

The present invention is directed to a method of treating one or more of the following disease and/or conditions, which comprises administering to a patient in need thereof the compound H-g(b)-D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2, where the Cysteines are bonded by a disulfide bond, or a pharmaceutically acceptable salt thereof, most preferably the acetate salt of the compound, in the treatment of certain diseases and/or conditions such as gastroenterological conditions and/or diseases, endocronological diseases and/or conditions, various types of cancers and conditions associated with cancer such as cancer cachexia and in the treatment of hypotension and panic attacks.

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 853 371 A (COY DAVID H ET AL) 1 August 1989 (1989-08-01) cited in the application column 1, line 59 - line 60 column 2, line 56 column 4, line 12 - line 29 claims 1,3-13 (Subjects 1, 2) ---	1-5
X	US 5 688 530 A (BODMER DAVID ET AL) 18 November 1997 (1997-11-18) column 5, compound f) column 7, line 22 - line 42 (Subjects 1, 2) --- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 May 2000	13.06.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Teyssier, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/US 99/17294

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P19/08 A61P25/18 A61P35/00 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 08529 A (KASPRZYK PHILIP G ;BIOMEASURE INC (US); CULLER MICHAEL D (US)) 5 March 1998 (1998-03-05) page 8, line 32 claims 1,2,6,29,38,85,86,137-141 (Subject 1) ---	1,2,5
X	WO 98 10786 A (COHEN YAROM) 19 March 1998 (1998-03-19) page 4, line 11 - line 29 claims 1,7,10,49,52-54,58 (Subject 1) --- -/--	1-3,5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 May 2000	13. 06. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl. Fax: (+31-70) 340-3016	Teyssier, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MOTTET C ET AL: "Hemodynamic effects of the somatostatin analog lanreotide in humans: placebo-controlled, cross-over dose-ranging Echo-Doppler study." HEPATOLOGY, vol. 27, no. 4, April 1998 (1998-04), pages 920-925, XP000870061 abstract (Subject 1) ---	1-3,5
X	SOBHANI I ET AL: "Lanreotide inhibits human jejunal secretion induced by prostaglandin E1 in healthy volunteers." BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, vol. 41, no. 2, February 1996 (1996-02), pages 109-114, XP000870052 page 111, first paragraph of Discussion page 113, last paragraph (Subject 1) ---	1-5
X	US 5 506 339 A (COY DAVID H ET AL) 9 April 1996 (1996-04-09) column 2, line 27-32 column 3, line 25 column 4, line 46 -column 5, line 16 (Subjects 1, 2) ---	1-5
Y	MOSDELL K W ET AL: "Emerging indications for octreotide therapy, Part 1." AMERICAN JOURNAL OF HOSPITAL PHARMACY, vol. 51, no. 9, 1 May 1994 (1994-05-01), pages 1184-1192, XP000866264 the whole document (Subjects 1, 2, 5) ---	1-5
Y	KHOO D ET AL: "Palliation of malignant intestinal obstruction using octreotide" EUROPEAN JOURNAL OF CANCER, vol. 30A, no. 1, 1994, pages 28-30, XP000866064 page 30, column 1, line 11 - line 16 (Subject 1) ---	1-5
Y	HASLER W ET AL: "ROLE OF THE PYLORUS IN THE PREVENTION OF DUODENO-GASTRIC REFLUX EFFECTS OF THE SOMATOSTATIN ANALOG." GASTROENTEROLOGY, vol. 100, no. 5, 19 - 22 May 1991, page A448 XP000866191 cited in the application the whole document (Subject 1) --- -/--	1,2,5

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ONO, MASASHI ET AL: "Effects of octreotide acetate treatment for scleroderma bowel." KAWASAKI MEDICAL JOURNAL, vol. 22, no. 4, 1996, pages 233-237, XP000866213 the whole document (Subject 1)	1,2,5
Y	PAVLOVIC M. ET AL: "Regression of sclerodermatous skin lesions in a patient with carcinoid syndrome treated by octreotide." ARCHIVES OF DERMATOLOGY, vol. 131, no. 10, October 1995 (1995-10), page 1207-1209 XP000866063 the whole document (Subject 1)	1,2,5
Y	KIRK J M W ET AL: "Somatostatin analogue in short term management of hyperinsulinism" ARCHIVES OF DISEASE IN CHILDHOOD, vol. 63, no. 12, 1988, page 1493-1494 XP002053035 the whole document (Subject 1)	1-5
P,X	WO 98 51332 A (SOD CONSEILS RECH APPLIC ;CAWTHORNE MICHAEL ANTHONY (GB); SENNITT) 19 November 1998 (1998-11-19) page 4, line 20 - line 27 (Subject 1) claims 1-23,27,21-35	1,2,5
X	RIEU M ET AL: "Paradoxical effect of somatostatin analogues on the ectopic secretion of corticotropin in two cases of small cell lung carcinoma." HORMONE RESEARCH, vol. 39, no. 5-6, November 1993 (1993-11), pages 207-212, XP000907231 abstract (Subject 2)	1,2,5
X	CHANSON P: "Traitements médicamenteux des adénomes hypophysaires." REVUE DU PRATICIEN, vol. 46, 15 June 1996 (1996-06-15), pages 1509-1513, XP000907252 pages 1312-1313, "Traitement médical des adénones non fonctionnels et des adénomes gonadotropes" - "Conclusion" (Subject 2)	1,2,5

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANTHONY L B ET AL: "Case report: lanreotide in the management of hypercalcemia of malignancy." AMERICAN JOURNAL OF THE MEDICAL SCIENCES, vol. 309, no. 6, June 1995 (1995-06), pages 312-314, XP000867465 the whole document (Subject 2) ---	1,2,5
A	ZEILKE A ET AL: "Octreotide: Effective treatment for hyperparathyroidism? A prospective, randomized, controlled clinical trial." SURGERY (ST LOUIS), vol. 121, no. 6, June 1997 (1997-06), pages 606-610, XP000907227 abstract: Conclusions (Subject 2) ---	1,5
T	KANG S & MISHKIN F S: "Visualization of Paget's disease during somatostatin receptor scintigraphy." CLINICAL NUCLEAR MEDICINE, vol. 24, no. 11, November 1999 (1999-11), pages 900-902, XP000907230 the whole document (Subject 2) ---	1,5
Y	BARTLETT D L ET AL: "Reversal of tumor-associated hyperglucagonemia as treatment for cancer cachexia." SURGERY (ST LOUIS), vol. 118, no. 1, July 1995 (1995-07), pages 87-97, XP000907234 abstract page 93, column 1, line 38 -column 2, line 2 page 96, column 1, line 13 - line 33 (Subject 3) ---	1-3,5
Y	JAFFRAIN-REA ML ET AL: "Visual improvement during octreotide therapy in a case of episellar meningioma." CLINICAL NEUROLOGY AND NEUROSURGERY, vol. 100, no. 1, March 1998 (1998-03), pages 40-43, XP000907228 page 42, column 2 (Subject 3) --- -/--	1-3,5

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SRKALOVIC G ET AL: "EVALUATION OF RECEPTORS FOR SOMATOSTATIN IN VARIOUS TUMORS USING DIFFERENT ANALOGS" JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 70, no. 3, March 1990 (1990-03), pages 661-669, XP000907224 page 668 (Subject 3) ---	1-3,5
Y	HOELDTKE R D ET AL: "Treatment of orthostatic hypotension with midodrine and octreotide." JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 83, no. 2, February 1998 (1998-02), pages 339-343, XP000907222 pages 342-343, "Discussion" (Subject 5) ---	1,2,5
Y	WECKBECKER G ET AL: "SOMATOSTATIN ANALOGS FOR DIAGNOSIS AND TREATMENT OF CANCER" PHARMACOLOGY AND THERAPEUTICS, vol. 60, no. 2, 1994, pages 245-264, XP002072560 page 246, paragraph 2 page 248, paragraph 4 page 257, paragraph 3 (Subjects 1, 3, 5) ---	1-5
Y	LAMRANI A ET AL: "Effects of lanreotide, a somatostatin analogue, on postprandial gastric functions and biliopancreatic secretions in humans." BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, vol. 43, no. 1, January 1997 (1997-01), pages 65-70, XP000870053 page 68, first paragraph of Discussion (Subjects 1, 5) ---	1-5
Y	WOLTERING E A ET AL: "DETECTION OF OCCULT GASTRINOMAS WITH IODINE 125-LABELED LANREOTIDE AND INTRAOPERATIVE GAMMA-DETECTION" SURGERY, vol. 116, no. 6, December 1994 (1994-12), pages 1139-1147, XP000866097 page 1139 -page 1140, column 1, line 19 (Subjects 1, 3) -----	1-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/17294

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-4 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1,5 partially, 2-4 totally for subjects 1, 2, 3 and 5 as defined

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-5 partially

Method of treatment using lanreotide and pharmaceutical composition comprising lanreotide acetate for the treatment of systemic sclerosis, pancreatic pseudocysts and ascites, VIPoma, neisoblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison syndrome, hypersecretory diarrhea, scleroderma, irritable bowel syndrome, upper gastrointestinal bleeding, postprandial portal veinous hypertension and complications of portal hypertension, small bowel obstruction and duodenogastric reflux.

2. Claims: 1-5 partially

Method of treatment using lanreotide and pharmaceutical composition comprising lanreotide acetate for the treatment of Cushing syndrome, gonadotropinoma, hyperparathyroidism, diabetic neuropathy, macular degeneration, hypercalcemia of malignancy and Paget's disease.

3. Claims: 1-3, 5 all partially

Method of treatment using lanreotide and pharmaceutical composition comprising lanreotide acetate for the treatment of meningioma and cancer cachexia.

4. Claim : 1 2 5 all partially

Method of treatment using lanreotide and pharmaceutical composition comprising lanreotide acetate for the treatment of psoriasis.

5. Claim : 1 2 5 all partially

Method of treatment using lanreotide and pharmaceutical composition comprising lanreotide acetate for the treatment of hypotension.

6. Claim : 1 2 5 all partially

Method of treatment using lanreotide and pharmaceutical composition comprising lanreotide acetate for the treatment of panic attacks.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/17294

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4853371 A	01-08-1989	AT 93866 T	15-09-1993
		CA 1338302 A	30-04-1996
		DE 3883649 D	07-10-1993
		DE 3883649 T	16-12-1993
		EP 0298732 A	11-01-1989
		ES 2058290 T	01-11-1994
		JP 1070500 A	15-03-1989
		JP 2809403 B	08-10-1998
		AU 602657 B	25-10-1990
		AU 6207686 A	19-03-1987
		CA 1338301 A	30-04-1996
		DK 435186 A	13-03-1987
		EP 0214872 A	18-03-1987
		FI 863680 A,B,	13-03-1987
		GR 862206 A	31-12-1986
		IE 59556 B	09-03-1994
		JP 2563278 B	11-12-1996
		JP 62116594 A	28-05-1987
		NO 174809 B	05-04-1994
		NZ 217509 A	26-04-1989
		PT 83359 A,B	01-10-1986
US 5688530 A	18-11-1997	US 5538739 A	23-07-1996
		AT 402503 B	25-06-1997
		AT 151591 A	15-10-1996
		AU 650277 B	16-06-1994
		AU 8143091 A	27-02-1992
		CA 2048200 A	02-02-1992
		CH 683772 A	13-05-1994
		CY 1986 A	05-09-1997
		DE 4124468 A	06-02-1992
		EP 0469520 A	05-02-1992
		EP 0816413 A	07-01-1998
		ES 2112259 T	01-04-1998
		FI 913641 A	02-02-1992
		FR 2665453 A	07-02-1992
		GB 2246573 A,B	05-02-1992
		GR 3026322 T	30-06-1998
		HK 11797 A	14-02-1997
		HU 59837 A	28-07-1992
		IE 66185 B	13-12-1995
		IL 99007 A	29-12-1994
		IT 1252944 B	05-07-1995
		JP 6041279 A	15-02-1994
		LU 87985 A	15-02-1993
		NZ 239184 A	27-09-1994
		PT 98491 A,B	30-06-1992
		ZA 9106070 A	28-04-1993
		HU 217117 B	29-11-1999
		US 5639480 A	17-06-1997
		US 5876761 A	02-03-1999
		AT 406225 B	27-03-2000
		AT 144090 A	15-08-1999
		AU 687553 B	26-02-1998
		AU 2332195 A	07-09-1995
		AU 641407 B	23-09-1993
		AU 5874690 A	10-01-1991
		BE 1004486 A	01-12-1992

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/17294

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5688530 A		CA 2020477 A	08-01-1991
		CH 685230 A	15-05-1995
		CH 686226 A	15-02-1996
		CH 686252 A	15-02-1996
		CY 1844 A	08-03-1996
		CY 1965 A	04-07-1997
		DE 4021517 A	17-01-1991
		DK 162590 A	08-01-1991
		FI 991120 A	17-05-1999
		FR 2649319 A	11-01-1991
WO 9808529 A	05-03-1998	AU 3215597 A	19-03-1998
		AU 4149097 A	19-03-1998
		CN 1229357 A	22-09-1999
		EP 0938328 A	01-09-1999
		PL 331922 A	16-08-1999
		WO 9808528 A	05-03-1998
WO 9810786 A	19-03-1998	AU 4133997 A	02-04-1998
US 5506339 A	09-04-1996	AT 140237 T	15-07-1996
		CA 2046594 A	09-06-1991
		DE 69027767 D	14-08-1996
		DE 69027767 T	02-01-1997
		DK 457888 T	12-08-1996
		EP 0457888 A	27-11-1991
		ES 2091907 T	16-11-1996
		GR 3020513 T	31-10-1996
		JP 2925321 B	28-07-1999
		JP 4505456 T	24-09-1992
		PT 96135 A,B	30-09-1991
		WO 9109056 A	27-06-1991
		ZA 9009896 A	25-09-1991
WO 9851332 A	19-11-1998	AU 8019898 A	08-12-1998
		EP 0980253 A	23-02-2000